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The influence of tissue cross-talking on OA progression: role of nonsteroidal antiinflammatory drugs

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Summary

Osteoarthritis is increasingly recognized as a complex illness in which interrelationships between the different tissues of the joint are important. We are still some way from a complete understanding of the pathophysiologic and temporal relationships between bone, synovial tissue and cartilage. Recent evidence points to a significant role for cytokines and growth factors in osteoarthritis that leads to a preponderance of catabolic processes in the joint.

In-vitro culture of human cartilage has been used as a model to measure the effects of drugs used in the treatment of osteoarthritis on anabolic and catabolic processes. On this basis, the nonsteroidal antiinflammatory drugs can be categorized into one of three classes depending on whether they are inhibitory (e.g., indomethacin and naproxen), neutral (e.g., diclofenac, aspirin and piroxicam) or stimulatory (e.g., aceclofenac, tenidap and tolmetin) of glycosaminoglycan synthesis in chondrocytes. The marked differences between these nonsteroidal antiinflammatory drugs suggest that a mechanism other than cyclooxygenase inhibition is involved in their effects on glycosaminoglycan synthesis. Inhibition of IL-1β and the stimulation of growth factors are suggested as possible mechanisms.

Although the significance of these properties of nonsteroidal antiinflammatory drugs awaits confirmation in *in-vivo* and clinical situations, they do provide the clinician with a new parameter with which to choose therapy in osteoarthritis.

Key words: Osteoarthritis, Nonsteroidal antiinflammatory drugs, Cytokines, Growth factors.

The St Regis Hotel (New York, 23–24 May 1998) was the venue for opinion leaders in the field of rheumatology to air their views on the current clinical and basic research aspects of osteoarthritis (OA). The workshop provided a forum for presentations about the individual tissues involved in OA and more general discussions about the influence of tissue cross-talking on the progression of OA and on the role of nonsteroidal antiinflammatory drugs (NSAIDs). The aim of this summary is to recapitulate some of the points that were raised in the round table discussions.

We live in a global world

OA is a common disease characterized by localized damage to the synovial joint. The widely held dogma in early investigations into the mechanisms involved in OA was that if more mechanical load were put on a joint, the more the cartilage would be eroded. The precise cause of OA remains elusive. It is realized, however, that a complex interplay exists between all joint tissues and that OA is not solely related to the erosion of cartilage but that pathological changes to synovial and subchondral bone also occur. Indeed, it is associated with a sequence of clinical and pathological changes that occur in response to mechanical and biochemical stimuli and result in destruction of the articular cartilage, new bone formation at the joint margins and eventual failure of the joint.

Tissues, catabolism and anabolism

The cytokines are considered an interesting link in OA since they are produced by many of the cells present in the OA joint. They are responsible, in part, for the changes seen in cartilage damage, the synovial membrane, subchondral bone and osteophyte formation.

In the normal joint, a delicate balance of degradation and repair processes maintains the entirety of the cartilage matrix. In OA, this equilibrium is disrupted and the catabolic processes prevail leading to the loss of joint integrity. Changes in the metabolic activity, or perhaps in the phenotype, of chondrocytes are thought to play a role in this process. Even in severe OA, chondrocytes retain their ability to synthesize new glycosaminoglycans (GAGs), although this may be true of only a fraction of the cells. Local release of catabolic cytokines, particularly interleukin-1 beta (IL-1β), tumor necrosis factor–alpha (TNF-α) and IL-6, in response to tissue damage and inflammation can inhibit GAG synthesis and levels of these cytokines are known to be elevated in OA. The growth factors, transforming growth factor-beta (TGF-β) and insulin-like growth factor (IGF)-1 serve to inhibit the catabolic effects of these cytokines. Thus, the imbalance between the growth factors and the cytokines represents an important feature in the failure of the repair process. It is not known, however, at what stage in the repair process the damage becomes irreversible. Synovial inflammation is also a feature of OA. Evidence suggests that the synovial cells themselves contribute to the degradation of cartilage.

Whilst articular cartilage is being lost, changes are also occurring in the bone. Bone plays an important role in the remodeling at the osteochondral junction and this affects the joint shape and size. Radiological studies used in the diagnosis of OA of the knee indicate that the subchondral bone trabeculae become thickened, the joint space is

narrowed and small bony outgrowths (osteophytes) can be seen at the joint margins. These osteophytes, which contribute to the limitation of joint movement, are formed by proliferation of cartilaginous tissue followed by endochondral ossification; it has been suggested that TGF-β may be involved in this process. Pain is thought to be the result of synovial inflammation. However, severe pain may also result from engorgement of bone, subchondral ischaemia and also many other factors.

Cross-talk and progression

The concept of movement of growth factors and cytokines from bone to cartilage was brought into discussion. Pathological studies by Leon Sokoloff have demonstrated the presence of clefts or channels in the tidemark that appear early in OA. If these are a common feature, they set up a situation for cross-talk between bone and cartilage. It has further been indicated that subchondral bone in different parts of the joint, with and without OA, produces cytokines which cause different types of reaction on the cartilage. Thus, it is possible that bone is driving cartilage metabolism. Bone morphologic protein has been shown to have an anabolic effect on chondrocytes and may promote cartilage matrix formation. This implies that signals causing differentiation may be coming from the bone.

Using X-ray technology it is possible to show that, in early OA, sclerosis may have overtaken the joint per se but that changes in subchondral bone are patchy. Osteophytes tend to form where there is vascular invasion at the outer margins of the joint, which is also a region from where cartilage is lost. This further suggests the role of bone factors is driving other metabolic processes.

Multiple tissue types contribute to the development of OA. Once the actual OA process begins, it usually progresses to result in serious joint damage and the 'full-blown' clinical situation. However, it is important to define what is meant by progression. At present, the definitions are somewhat unclear. Progression may mean that patients require alternative pharmacotherapy; it may indicate that there is greater cartilage loss; it may suggest that there is a clinical progression of pain and disability; or it may relate to a radiographic change in joint structure. Until there is a recognized definition of progression, clinical outcome is probably one of the most important markers.

Clinical studies have shown some continuity between both bone and cartilage changes as OA progresses and experimental data suggests that there is cross-talk between these tissues. If the bone's response to injury and also if associations with bone proteins could be elucidated, it may be possible to identify factors associated with OA progression.

Models as vehicles to study OA

Basic science proceeds at an exponential rate of discovery and new mediators and pathways that may be relevant to OA are continually being discovered. *In-vitro* methods to investigate these parameters, and the beneficial (or otherwise) effects of particular drugs, may provide a swift method by which to assess the processes involved in OA and its treatment. However, are these types of *in-vitro* studies always relevant for the *in-vivo* situation?

A number of animal models of OA have been developed and these can provide some useful information about joint mechanics and the destructive processes involved. However, there are still doubts about their relevancy to a disease process that takes years to develop in humans. Whatever the animal, and whatever the method for eliciting a process that is similar to human OA, all such studies must be equivalent to studies in humans in terms of predetermined outcome measures and statistical viability.

Studies using human cartilage cultured *in vitro* from the cartilage of patients taking NSAIDs have shown that some of these drugs (e.g., indomethacin, diclofenac and naproxen) have a deleterious effect, via inhibition of GAG synthesis, whilst others (e.g. aceclofenac, tenidap and tolmetin) stimulate GAG synthesis. It is not clear, however, whether these results translate to the same process *in vivo*. There is a series of problems associated with extrapolation from *in-vitro* to *in-vivo* situations.

Unfortunately, procedures for following the rate of change, non-invasively, in human joints with OA, in general remain unsatisfactory. There may be plasma or synovial fluid markers, such as keratan sulphate or hyaluronan, that can be used to follow changes, but these are not necessarily of real value. Moreover, although some drugs may have disease modifying properties, the capacity for determining the extent of the changes they may produce in the patient is far from complete.

The role of NSAIDs in OA treatment

The treatments currently available for OA afford only palliative care. The prescription of simple analgesics (acetaminophen) to reduce pain generally precedes treatment with NSAIDs. If these simple analgesics prove ineffective, NSAIDs may be prescribed either alone or in combination with an analgesic. Although NSAIDs are clinically important for relieving the symptoms of pain and inflammation, their mechanisms of action are not yet fully understood.

The NSAIDs have been categorized with respect to their actions *in vitro* on cartilage:

- Those which can stimulate GAG synthesis (such as aceclofenac, tenidap and tolmetin)
- Those without a significant effect (such as diclofenac, aspirin and piroxicam)
- Those which significantly inhibit GAG synthesis (such as naproxen, ibuprofen and indomethacin)

Although NSAIDs are efficacious for acute and chronic pain, their role in the treatment of OA is not completely resolved and there is still much to be learned. It is clear that there are differences between NSAIDs. Although all NSAIDs inhibit the production of PGE_2, some also inhibit matrix component synthesis. There may be other mechanisms, in addition, which explain the different properties of different NSAIDs. Moreover, although there is data comparing NSAIDs to one another, there is very little data that compares NSAIDs to simple analgesics. Each NSAID therefore needs to be evaluated separately for its effectiveness in treatment.

The ideal NSAID

Although imperfect, NSAIDs are the most widely used drug therapy in OA. There are other possibilities on the horizon, but for now, the therapeutic challenge is to select the ideal NSAID. From the cartilage perspective the ideal

NSAID would stimulate (organized) chondroformation, decrease chondroresorption and also decrease the synthesis of catabolic cytokines.

The future

It is clear that considerable progress has been made towards greater understanding of the underlying mechanisms involved in OA. There are, nevertheless, several questions that remain unanswered. Progression and tissue cross-talking in OA were the main themes of the workshop, but one aspect of this complex interaction was perhaps overlooked. Progression was alluded to as being the advancement of a series of pathological features resulting from aberrant biochemistry in the joint. However, what causes the joint to progress from dormancy to an active site of such processes and whether there is any way in which this can be accurately evaluated need to be further examined.

The role of NSAIDs was brought into question and alternative therapies were discussed. However, until such time as alternative therapies can be proven to be effective *in vitro*, in animal models *in vivo* and in clinical trials, NSAIDs look set to remain one of the mainstays of treatment for OA and, perhaps most importantly, they are currently the patients' preferred choice. Certainly, if in the future, NSAIDs that demonstrate the same anabolic effects on cartilage *in vivo* as they do *in vitro* could represent a significant therapeutic advantage. Well designed, follow-up studies of patients taking these types of drugs will provide some of the answers. For the immediate future, whether prescribed alone or in combination with other analgesics or gastroprotective drugs the treatment of OA with NSAIDs is fairly secure.

Conclusions

OA is a common disorder characterized by damage to the structures within synovial joints. Damage can occur to bone, synovium and cartilage and the inter-relationships between these tissues is complex. The exact sequence of pathophysiological events in OA remains unclear; the temporal relationship between bone damage, chronic inflammation of synovial tissue and cartilage erosion is unknown.

In OA, the balance between anabolic and catabolic processes is disrupted and catabolic processes predominate; cytokines and growth factors respectively are believed to be involved in the imbalance in catabolic and anabolic pathways.

The progressive nature of OA is clinically, radiologically, and histologically evident although a clear marker of the disease does not exist. In the absence of a definitive marker for progression, clinical outcome is regarded as the most important indicator.

A variety of measures of OA evolution and progression have been developed. Animal models have pointed to potential pathophysiological mechanisms, although the application of the results of these studies to the clinical situation remains controversial. New data, using cultured human cartilage *in vitro* or *ex vivo*, may represent a promising approach while results from *in vivo* studies are awaited.

On the basis of *in-vitro* studies, NSAIDs have been classified into three groups according to whether they are inhibitory (e.g., indomethacin and naproxen), neutral (e.g., diclofenac, aspirin and piroxicam) or stimulatory (e.g., aceclofenac, tenidap and tolmetin) of glycosaminoglycan synthesis in chondrocytes. There are clear differences between NSAIDs in these studies which may be related to their differential effects on cytokines and/or the chondrocyte metabolic processes which they control. In this sense, the inhibition of IL-1β and the stimulation of growth factors have been suggested as possible explanations of the differential activity on cartilage of aceclofenac, a well-investigated NSAID in this field, with promising results.

It is important to evaluate the effects of the drugs selected for treating OA on the pathophysiological processes that occur in this disease: bone changes, synovial inflammation and particularly cartilage destruction. In the future, new techniques will help to clarify the evolution of the disease, as well as the positive, negative or neutral effects drugs may have on OA progression. In addition to the usual concern for efficacy and safety, practitioners should bear in mind their effect on the tissues involved in the disease.

OA is an active process with the potential to repair. Therefore, treatments that may stimulate these potential repair mechanisms may present an advance over those which do not.